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10/576,575	07/14/2008	Robyn Lynne Ward	037775-0107	4121

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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,575	WARD ET AL.	
	Examiner	Art Unit	
	Amanda Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :4/20/06, 10/1/07, 11/29/07, 1/6/10.

DETAILED ACTION

1. Claims 1-9 are currently pending and have been examined herein.

Information Disclosure Statement

2. The information disclosure statement filed April 20, 2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Further it is noted that the references cited on this IDS were also cited in the Search Report for PCT/AU2004/001434 mailed November 18, 2004. Typically the examiner will consider the documents cited in an international search in a PCT national stage application when the Form PCT/DO/EO/903 indicates that both the international search report and the copies of the documents are present in the national stage file (MPEP 609.03). However in the instant case receipt of such copies is not indicated on the PCT/DO/EO/903 form. Once the copies are provided they will be considered.

The information disclosure statement (IDS) submitted on October 1, 2007 has been received. The references listed in the IDS have been reviewed as indicated on the 1449, and a copy is attached herein. Please note that there was a typographical error on the IDS, WO 01/75172 A2 is actually WO 01/75175 A2. Also only the abstract of WO 2005/001141 has been considered since only the abstract has been provided.

The information disclosure statement (IDS) submitted on November 29, 2007 has been received. The references listed in the IDS have been reviewed as indicated on the 1449, and a copy is attached herein.

The information disclosure statement (IDS) submitted on January 6, 2010 has been received. The references listed in the IDS have been reviewed as indicated on the 1449, and a copy is attached herein.

Specification

3. The abstract of the disclosure is objected to because the form and legal phraseology often used in patent claims, such as “means" and “said”, should be avoided. The instant abstract recites the following phrases: "said assay", "said individual", "said population of cells", "said gene", and “said disease". Correction is required. See MPEP § 608.01(b).

The disclosure is objected to for having a typographical error. The heading “Example 2” on page 10 of the specification should be “Example 1” since the specification contains two working examples. The first working example begins on page 10 and the second working example (which also uses the heading “Example 2”) begins on page 14. Appropriate correction is required.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waki (American Journal of Pathology 8/2002 Vol 161 No 2 pages 399-403) in view of Okamoto (Proc. Natl. Acad Sci. 5/1997 Vol 94 pages 5367-5371).

Regarding Claim 1 Waki teaches investigating the promoter methylation status of the hMLH1 and p16 genes. Waki teaches that 94 gastric cancer samples and their matching non neoplastic gastric tissues were obtained at surgery from 94 patients (page 400, col 1). Thus Waki teaches isolating a population of cells from normal tissue (the

non neoplastic gastric tissue) of 94 patients. Waki teaches that genomic DNA was extracted and then the samples were treated with bisulfite and amplified via methylation specific PCR (page 400, col 1). Waki teaches that methylation of hMLH1 and p16 was present in both neoplastic and non neoplastic gastric epithelia as follows: 32% (30 of 94) and 24% (23 of 94) for hMLH1 and 22% (21 of 94) and 44% (41 of 94) for p16 (page 400, col 2). In the instant case both hMLH1 and p16 are associated with gastric cancer since Waki teaches that in gastric cancers the loss of function of hMLH1 and p16 is linked to hypermethylation of CpG islands within their promoters (page 399, col 2). Further it is noted that hMLH1 and p16 are both genes that are not involved in parental imprinting (not subject to normal parent of origin specific expression). Additionally Waki states that detection of hMLH1 methylation in non neoplastic gastric epithelia may be useful for screening patients who may be at risk of developing gastric cancer (abstract).

Regarding Claim 4 Waki teaches a method wherein the epimutation is DNA methylation (abstract).

Regarding Claim 5 Waki teaches that methylation in the promoter region of hMLH1 correlates well with gene silencing (page 402, col 2). Thus Waki teaches a method wherein the epimutation (methylation) is present in the promoter region of the hMLH1 gene and is associated with transcriptional silencing of the hMLH1 gene.

Regarding Claim 6 Waki teaches a method wherein the epimutation (methylation) is associated with cancer since Waki teaches that in gastric cancers the loss of function of hMLH1 and p16 is linked to hypermethylation of CpG islands within their promoters (page 399, col 2).

Regarding Claim 7 Waki teaches a method wherein the epimutation (methylation) is present in a tumor suppressor gene since hMLH1 is a tumor suppressor gene (abstract).

Regarding Claim 8 Waki teaches a method wherein the epimutation is present in a gene selected from hMLH1 or p16 (abstract).

Regarding Claim 9 Waki teaches a method wherein the epimutation is present in hMLH1 (abstract).

Waki does not teach a method of quantitatively determining the frequency of epimutation of a particular gene in said population of cells (clm 1). In the instant case this is being interpreted as determining how many cells have the methylated gene in the population of cells. Waki does not teach a method wherein the normal tissue is normal peripheral blood (clms 2 & 3).

However Okamoto teaches a method wherein the methylation status of a part of the H19 promoter was examined in the unaffected adjacent kidney and peripheral blood of Wilms tumor patients to determine whether aberrant methylation of H19 was present in normal tissues (page 5368, col 1). Okamoto teaches that H19 methylation was quantified by determining the percentage of cells with H19 biallelic methylation. This percentage was calculated by using 100(x-1)/(x+1), where x is the methylated H19/unmethylated H19 allele ratio (page 5368, col 1). Okamoto further teaches that the high proportion of epigenetically modified cells among normal tissues indicates that the epigenetic error occurred very early in development, before the onset of Wilms tumor (abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Waki by quantitatively determining the number of times the hMLH1 and p16 genes are methylated in the population of cells from normal tissue as suggested by Okamoto. In the instant case Okamoto teaches that the high proportion of epigenetically modified cells among normal tissues indicates that the epigenetic error occurred very early in development, before the onset of Wilms tumor (abstract). Waki teaches that detection of hMLH1 methylation in non neoplastic gastric epithelia may be useful for screening patients who may be at risk of developing gastric cancer (abstract). Thus one of skill in the art would have been motivated to determine the frequency of methylation of a particular gene in a population of cells in order to screen patients who may be at risk of developing cancer before the onset of a tumor. Further it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Waki by isolating the population of cells form normal peripheral blood as suggested by Okamoto. In the instant case Okamoto teaches that increased H19 methylation status was detected in one of four blood samples from Wilms tumor patients (page 5368, col 1). As such one of skill in the art would have been motivated to isolate a population of cells from normal peripheral blood in order to achieve benefit of noninvasive detection of cancer. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore the invention as a whole was prima facie obvious to one or ordinary skill in the art at the time the invention was made, as evidenced by the references.

6. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong (Cancer Research 1/1999 Vol 59 pages 71-73) in view of Okamoto (Proc. Natl. Acad Sci. 5/1997 Vol 94 pages 5367-5371).

Regarding Claim 1 Wong teaches that they detected aberrant p16 methylation in samples derived from liver cancer patients. Wong teaches that they recruited 22 hepatocellular carcinoma (HCC) patients. Peripheral blood and resection HCC specimens were obtained from each patient. Peripheral blood from each patient was collected into either an EDTA tube or plain tube for the isolation of plasma or serum. Blood samples were centrifuged and plasma and serum were carefully removed from the EDTA-containing and plain tubes. The buffy coat fraction from the EDTA containing tubes was also collected to study the presence of circulating tumor cells in the peripheral blood (page 71, col 1-2). Thus Wong teaches isolating a population of cells from normal tissue wherein the normal tissue is normal peripheral blood. Here it is noted that while the plasma and serum samples do not contain cells the buffy coat fraction contains white blood cells and platelets. Wong teaches that DNA was extracted from the plasma and serum samples using the QIAamp Blood kit and DNA was extracted from the buffy coat samples using a Nucleon BACC2 DNA extraction kit. The DNA was then treated with bisulfite and amplified via methylation specific PCR (page 71, col 2). Wong teaches that a total of 16 of 22 (73%) tumors were found to have methylated p16 sequences. For the 16 cases with methylated p16 sequences in tumors, MSP was able to detect the same change in the plasma and serum samples of 13

cases (81%). In the 15 cases involving peripheral plasma samples, buffy coat samples were also available. MSP analysis was positive in two buffy coat samples from two patients with tumoral p16 methylation. MSP was negative in the remaining 13 cases. In the instant case p16 is associated with HCC since Wong teaches that inactivation of a tumor suppressor gene, p16, which is important in the regulation of cell cycling, has recently been described in a significant proportion of patients with HCC (page 71, col 1). Here it is noted that p16 is not involved in parental imprinting (not subject to normal parent of origin specific expression).

Regarding Claims 2 and 3 Wong teaches isolating a population of cells (the buffy coat) from normal peripheral blood (page 71, col 1-2).

Regarding Claim 4 Wong teaches a method wherein the epimutation is DNA methylation (abstract).

Regarding Claim 5 Wong teaches that methylation in the promoter region of p16 is involved in inactivation of the p16 gene (page 71, col 1). Thus Wong teaches a method wherein the epimutation (methylation) is present in the promoter region of the p16 gene and is associated with transcriptional silencing of the p16 gene.

Regarding Claim 6 Wong teaches a method wherein the epimutation (methylation) is associated with cancer since Wong teaches that inactivation of a tumor suppressor gene, p16, which is important in the regulation of cell cycling, has recently been described in a significant proportion of patients with HCC (page 71, col 1).

Regarding Claim 7 Wong teaches a method wherein the epimutation (methylation) is present in a tumor suppressor gene since p16 is a tumor suppressor gene (page 71, col 1).

Regarding Claim 8 Wong teaches a method wherein the epimutation is present in the p16 gene (abstract).

Wong does not teach a method of quantitatively determining the frequency of epimutation of a particular gene in said population of cells (clm 1). In the instant case this is being interpreted as determining how many cells have the methylated gene in the population of cells.

However Okamoto teaches a method wherein the methylation status of a part of the H19 promoter was examined in the unaffected adjacent kidney and peripheral blood of Wilms tumor patients to determine whether aberrant methylation of H19 was present in normal tissues (page 5368, col 1). Okamoto teaches that H19 methylation was quantified by determining the percentage of cells with H19 biallelic methylation. This percentage was calculated by using 100(x-1)/(x+1), where x is the methylated H19/unmethylated H19 allele ratio (page 5368, col 1). Okamoto further teaches that the high proportion of epigenetically modified cells among normal tissues indicates that the epigenetic error occurred very early in development, before the onset of Wilms tumor (abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Wong by quantitatively determining the number of times the p16 gene is methylated in the population of cells

from normal tissue as suggested by Okamoto. In the instant case Okamoto teaches that the high proportion of epigenetically modified cells among normal tissues indicates that the epigenetic error occurred very early in development, before the onset of Wilms tumor (abstract). Thus one of skill in the art would have been motivated to determine the frequency of methylation of a particular gene in a population of cells in order to screen patients who may be at risk of developing cancer before the onset of a tumor. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore the invention as a whole was prima facie obvious to one or ordinary skill in the art at the time the invention was made, as evidenced by the references.

7. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wong (Cancer Research 1/1999 Vol 59 pages 71-73) in view of Okamoto (Proc. Natl. Acad Sci. 5/1997 Vol 94 pages 5367-5371) as applied to claims 1 and 7-8 above and in further view of Waki (American Journal of Pathology 8/2002 Vol 161 No 2 pages 399-403).

Wong teaches that they detected aberrant p16 methylation in samples derived from liver cancer patients. Wong teaches that they recruited 22 hepatocellular carcinoma (HCC) patients. Peripheral blood and resection HCC specimens were obtained from each patient. Peripheral blood from each patient was collected into either

an EDTA tube or plain tube for the isolation of plasma or serum. Blood samples were centrifuged and plasma and serum were carefully removed from the EDTA-containing and plain tubes. The buffy coat fraction from the EDTA containing tubes was also collected to study the presence of circulating tumor cells in the peripheral blood (page 71, col 1-2). Thus Wong teaches isolating a population of cells from normal tissue wherein the normal tissue is normal peripheral blood. Here it is noted that while the plasma and serum samples do not contain cells the buffy coat fraction contains white blood cells and platelets. Wong teaches that DNA was extracted from the plasma and serum samples using the QIAamp Blood kit and DNA was extracted from the buffy coat samples using a Nucleon BACC2 DNA extraction kit. The DNA was then treated with bisulfite and amplified via methylation specific PCR (page 71, col 2). Wong teaches that a total of 16 of 22 (73%) tumors were found to have methylated p16 sequences. For the 16 cases with methylated p16 sequences in tumors, MSP was able to detect the same change in the plasma and serum samples of 13 cases (81%). In the 15 cases involving peripheral plasma samples, buffy coat samples were also available. MSP analysis was positive in two buffy coat samples from two patients with tumoral p16 methylation. MSP was negative in the remaining 13 cases. In the instant case p16 is associated with HCC since Wong teaches that inactivation of a tumor suppressor gene, p16, which is important in the regulation of cell cycling, has recently been described in a significant proportion of patients with HCC (page 71, col 1). Here it is noted that p16 is not involved in parental imprinting (not subject to normal parent of origin specific expression).

Regarding Claim 7 Wong teaches a method wherein the epimutation (methylation) is present in a tumor suppressor gene since p16 is a tumor suppressor gene (page 71, col 1).

Regarding Claim 8 Wong teaches a method wherein the epimutation is present in the p16 gene (abstract).

Wong does not teach a method of quantitatively determining the frequency of epimutation of a particular gene in said population of cells (clm 1). In the instant case this is being interpreted as determining how many cells have the methylated gene in the population of cells.

However Okamoto teaches a method wherein the methylation status of a part of the H19 promoter was examined in the unaffected adjacent kidney and peripheral blood of Wilms tumor patients to determine whether aberrant methylation of H19 was present in normal tissues (page 5368, col 1). Okamoto teaches that H19 methylation was quantified by determining the percentage of cells with H19 biallelic methylation. This percentage was calculated by using 100(x-1)/(x+1), where x is the methylated H19/unmethylated H19 allele ratio (page 5368, col 1). Okamoto further teaches that the high proportion of epigenetically modified cells among normal tissues indicates that the epigenetic error occurred very early in development, before the onset of Wilms tumor (abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Wong by quantitatively determining the number of times the p16 gene is methylated in the population of cells

from normal tissue as suggested by Okamoto. In the instant case Okamoto teaches that the high proportion of epigenetically modified cells among normal tissues indicates that the epigenetic error occurred very early in development, before the onset of Wilms tumor (abstract). Thus one of skill in the art would have been motivated to determine the frequency of methylation of a particular gene in a population of cells in order to screen patients who may be at risk of developing cancer before the onset of a tumor.

Neither Wong nor Okamoto teach a method wherein the epimutation is present in the hMLH1 gene (clm 9).

However Waki teaches that they investigated the promoter methylation status of the hMLH1 gene. Waki teaches that 94 gastric cancer samples and their matching non neoplastic gastric tissues were obtained at surgery from 94 patients (page 400, col 1). Thus Waki teaches isolating a population of cells from normal tissue (the non neoplastic gastric tissue) of 94 patients. Waki teaches that genomic DNA was extracted and then the samples were treated with bisulfite and amplified via methylation specific PCR (page 400, col 1). Waki teaches that methylation of hMLH1 was present in both neoplastic and non neoplastic gastric epithelia as follows: 32% (30 of 94) and 24% (23 of 94).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Wong and Okamoto by further detecting methylation of hMLH1 as suggested by Waki. It is noted that Waki teaches that hypermethylation of both p16 and hMLH1 have been implicated in gastric cancer and both are tumor related genes (page 399, col 1 to 2). Therefore one of skill in the art would have been motivated to determine if hypermethylation of hMLH1 is also

involved in other cancers. Further Wong teaches that their approach can be applied to a wide variety of other tumors and other genes which that have been shown to exhibit aberrant methylation (page 72, col 2). From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore the invention as a whole was prima facie obvious to one or ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda Shaw whose telephone number is (571)272-8668. The examiner can normally be reached on Mon-Thurs 8:00 TO 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amanda Shaw/
Examiner 1634